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Association of enlarged perivascular spaces and anticoagulant-related intracranial hemorrhage

Jonathan G Best MRCP[1], Carmen Barbato MD[1], Gareth Ambler PhD[2], Houwei Du MD[1,3], Gargi Banerjee PhD MRCP[1], Duncan Wilson PhD[1,], Clare Shakeshaft MSc[1], Hannah Cohen MD FRCP[4], Tarek A Yousry Dr Med Habil FRCR[5], Rustam Al-Shahi Salman PhD[6], Gregory Y H Lip FRCP[7], Henry Houlden MRCP[8], Martin M Brown FRCP[1], Keith W Muir MD FRCP[9], Hans Rolf Jäger MD FRCR[5], and David J Werring PhD FRCP[1], *on behalf of the Clinical Relevance of Microbleeds in Stroke (CROMIS-2) collaborators*

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[1]Stroke Research Center, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, London, UK

[2]Department of Statistical Science, University College London, London, UK

[3]Stroke Research Center, Department of Neurology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

[4]Haemostasis Research Unit, Department of Haematology, University College London, London, UK

[5]Lysholm Department of Neuroradiology and the Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, London, UK

[6]Center for Clinical Brain Sciences, School of Clinical Sciences, University of Edinburgh, Edinburgh, UK

[7]Liverpool Center for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, UK; Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[8]Department of Molecular Neuroscience, UCL Queen Square Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK

[9]Institute of Neuroscience & Psychology, University of Glasgow, Queen Elizabeth University Hospital, Glasgow, UK

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Corresponding author:

Professor David J Werring

d.werring@ucl.ac.uk

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Glossary:

ARWMC – age-related white matter changes; CAA – cerebral amyloid angiopathy; CMB – cerebral microbleed; FLAIR – fluid attenuation inversion recovery; GCA – global cortical atrophy; GRE – gradient recalled echo; HR – hazard ratio; ICH – intracerebral hemorrhage; IPAD – intra-mural periarterial drainage; OAC – oral anticoagulant; PVS – enlarged perivascular spaces; BGPVS – basal ganglia enlarged perivascular spaces; CSOPVS – centrum semiovale enlarged perivascular spaces; sICH – symptomatic intracranial hemorrhage

Coinvestigator Appendix - http://links.lww.com/WNL/B209

Abstract

Objective To investigate whether enlarged perivascular spaces within the basal ganglia or deep cerebral white matter are risk factors for intracranial hemorrhage in patients taking oral anticoagulants (OAC), independent of established clinical and radiological risk factors, we conducted a *post hoc* analysis of CROMIS-2 (AF), a prospective inception cohort study.

Methods Patients with atrial fibrillation and recent TIA or ischaemic stroke underwent standardised MR imaging prior to starting OAC. We rated basal ganglia (BGPVS) and centrum semiovale (CSOPVS) perivascular spaces, cerebral microbleeds (CMBs), white matter hyperintensities and lacunes. We dichotomized the PVS rating using a threshold of >10 PVS in the relevant region of either cerebral hemisphere. The primary outcome was symptomatic intracranial hemorrhage (sICH). We identified risk factors for sICH using Cox regression.

Results 1386 participants with available clinical and imaging variables were followed up for a mean of 2.34 years. 14 sICH occurred (11 intracerebral). In univariable analysis, diabetes, CMB presence, lacune presence and >10 BGPVS, but not CSOPVS, were associated with sICH. In a multivariable model incorporating all variables with significant associations in univariable analysis, >10 BGPVS (HR 8.96, 95% CI 2.41 – 33.4, p = 0.001) and diabetes (HR 3.91, 95% CI 1.34 – 11.4) remained significant risk factors for sICH.

Conclusion Enlarged BGPVS might be a novel risk factor for OAC-related ICH. The strength of this association and potential use in predicting ICH in clinical practice should be investigated in larger cohorts.

Introduction

Within the brain, the perivascular space is the compartment bounded by the wall of penetrating cerebral blood vessels and the glia limitans, which might facilitate fluid circulation and clearance of soluble waste, including amyloid-beta, from brain parenchyma [1-3]. In age and disease, perivascular spaces may enlarge and become MRI-visible, as fluid-filled structures most easily assessed within the basal ganglia and the centrum semiovale white matter. Cross-sectional studies of intracerebral haemorrhage (ICH) survivors have associated enlarged basal ganglia perivascular spaces (BGPVS) with deep ICH, increased white matter hyperintensity volume, and deep cerebral microhemorhages (CMBs), and enlarged centrum semiovale perivascular spaces (CSOPVS) with lobar ICH and cerebral amyloid angiopathy (CAA) [4-6]. In cognitively-impaired patients, BGPVS are associated with hypertension, deep CMBs and lacunes, and CSOPVS with lobar CMBS, cortical superficial siderosis and Alzheimer's disease [7-9].

Together, these data suggest that BGPVS might be markers of deep perforator arteriopathy, and CSOPVS of amyloid-beta pathology, including CAA. PVS might therefore also indicate increased ICH risk. A prospective study of patients with TIA or ischaemic stroke found an association between >20 BGPVS in either hemisphere and incident ICH, though this was not statistically significant when adjusted for vascular risk factors [10]. We wished to investigate this question in patients with atrial fibrillation taking oral anticoagulants (OAC) after ischaemic stroke or TIA. We hypothesized that BGPVS and CSOPVS would be associated with anticoagulant-related intracranial hemorrhage (OAC-ICH), independent of other

markers of cerebral small vessel disease linked to OAC-ICH, notably CMBs and white matter hyperintensities [11,12].

Methods

Study design

We conducted a *post hoc* analysis of the CROMIS-2 (AF) study, a multicenter prospective inception cohort study of the relationship between cerebral microbleeds and anticoagulant-related symptomatic intracranial hemorrhage. The design, full description of the cohort, and primary results of this study have been published elsewhere[11]. Briefly, we recruited adult patients with atrial fibrillation initiating oral anticoagulation after recent ischaemic stroke or TIA from 79 hospitals in the United Kingdom and one in the Netherlands, between August 2011 and July 2015. MR imaging was performed at baseline according to a standardised protocol, including axial T1- and T2 –weighted, coronal fluid-attenuated inversion recovery (FLAIR), diffusion-weighted, and T2*-weighted GRE sequences. To reduce selection bias, imaging was performed after study enrolment, and we only enrolled participants whose responsible clinician had already decided to treat with an anticoagulant. We followed up participants for 24 months using multiple overlapping methods, including postal questionnaires, telephone interviews, and hospital episode statistics. The primary outcome was symptomatic intracranial hemorrhage (sICH), defined as brain-imaging evidence of non-traumatic spontaneous intracranial hemorrhage with appropriate clinical symptoms.

Neuroimaging analysis

We analyzed participants' MR imaging for markers of cerebral small vessel disease according to STRIVE definitions [13]. Trained research fellows (JGB, DW, GB, HD)

performed ratings blinded to the occurrence of sICH during follow-up, using validated rating scales where available. One of two raters (GB, HD) rated PVS at the level of the basal ganglia and centrum semiovale separately, using a five-level scale which assigns a score of 0 to no visible perivascular spaces, 1 to 1 – 10, 2 to 11 – 20, 3 to >21 – 40, and 4 to >40 perivascular spaces [14]. We rated each hemisphere, unless prevented by the presence of a focal lesion, and used the higher of the two values. We rated cerebral microbleeds (CMBs) using the Microbleed Anatomical Rating Scale [15], and white matter hyperintensities using the Age-Related White Matter Changes (ARWMC) scale (DW) [16]. We identified and counted lacunes (GB, HD).

Given the possibility that enlarged perivascular spaces might predominantly reflect cerebral atrophy, one of two raters (GB, JGB) rated each participant's imaging using the simplified Pasquier Scale [17], which quantifies the global severity of cortical atrophy (GCA) on a four-level scale (0: no atrophy, 1: sulcal widening, 2: gyral volume loss, 3: 'knife-blade' atrophy). We used axial T1 or FLAIR images for rating if available, and inverted axial T2 images if not. When a significant focal lesion was present, we rated the non-lesioned hemisphere. When more than one rater rated a marker, we assessed inter-rater agreement on a random sample using Cohen's Kappa, weighted for ordinal variables.

Statistical analysis

We investigated the association between enlarged perivascular spaces and the hazard of symptomatic intracranial hemorrhage using Cox regression. As well as BGPVS and CSOPVS, we prespecified age, sex, clinical history of diabetes mellitus and clinical history of hypertension as clinical independent variables and ARWMC score, cerebral microbleeds, lacunes and GCA as additional imaging independent variables. We chose not to include cortical superficial siderosis (cSS) due to its very low prevalence in our study population.

Using a predetermined threshold previously associated with the presence of other small vessel disease markers [14] and incorporated into a validated composite small vessel disease score as representing moderate to severe PVS[18], we dichotomised perivascular space counts in our analysis as 0 – 10 or >10, equivalent to a PVS score of 0 – 1 and 2 – 4 respectively. We dichotomised cerebral microbleeds and lacunes as present or absent. We included the ARWMC score as a continuous variable. As very few participants received a GCA rating of three, we combined categories 2 and 3 to give a three-level ordinal variable comprising no atrophy (0), minor atrophy (1), and moderate-severe atrophy (2-3). To reduce the risk of overfitting, we initially performed univariable analysis for each variable, and included only variables with an association at the 20% level in our final multivariable analysis. We checked the proportional hazards assumption using visual inspection of log-log plots of the log cumulative hazard against log time and through post-estimation tests based on Schoenfeld residuals. We summarized our results graphically using plots of the Kaplan-Meier failure (1 – survival) function. Statistical analysis was performed using Stata version 15.0.

Standard Protocol Approvals, Registrations, and Patient Consents

The UK National Health Service Research Ethics Committee approved the CROMIS-2 study. Patients with capacity provided written informed consent. We obtained proxy written informed consent if patients lacked capacity to consent, following relevant local legislation.

Data Availability

We will share anonymized data on reasonable request, following consideration by the CROMIS-2 steering committee and execution of a data sharing agreement. Requests should be submitted to d.werring@ucl.ac.uk.

Results

The primary analysis of the CROMIS-2(AF) study included 1447 participants who met the main study inclusion criteria and had follow-up data available. Of these, 1386 participants (95.8%) had all additional variables of interest needed for this secondary analysis (*Figure 1)*. Participants excluded from our secondary analysis due to missing variables were more likely to be female and have hypertension. As other variables were comparable *(Table 1)* and the overall proportion of missing data was very low, we performed a complete case analysis. During 3251 participant-years of follow-up, 14 sICH occurred (11 intracerebral, two subdural, 1 subarachnoid). The median time from anticoagulation initiation to sICH was 272 days (IQR 211 – 657). Of the ten intracerebral haemorrhages for which data on location was available, two were deep, four were infratentorial, and four were lobar. *Table* 2 summarizes the clinical and radiological characteristics of participants with and without sICH during follow-up. Interrater agreement for dichotomized PVS score was excellent (k = 0.82) within the basal ganglia and substantial (k = 0.80) within the centrum semiovale (n = 50). Agreement for GCA rating was moderate (k = 0.53; n = 100), comparable to that in other existing literature [19]. We observed a weak correlation between GCA and BGPVS grade (Spearman's rho 0.17, 95% CI 0.12 – 0.22), but not CSOPVS grade (r = 0.04, 95% CI -0.01 – 0.01).

Univariable Cox regression showed associations between BGPVS, diabetes, lacune presence, and cerebral microbleed presence and sICH (*Table 3)*. We found no evidence of an association between CSOPVS and sICH. In a multivariable model incorporating diabetes, BGPVS, cerebral microbleed presence and lacune presence, we found strong evidence of an association with sICH for enlarged BGPVS and diabetes, and weak evidence of an association for cerebral microbleed presence. No evidence of an association was found for

lacune presence. *Figure 2* shows the cumulative incidence of sICH during study follow-up for participants with 0 – 10 and >10 BGPVS. The absolute rate of sICH in participants with >10 BGPVS was 1.38/100 participant-years (95% CI 0.69 – 2.47), compared to 0.12/100 participant-years (95% CI 0.025 – 0.36) in participants with 0 – 10 BGPVS.

Given the number of variables included in our multivariable model relative to the number of outcome events, we performed additional sensitivity analyses, testing each combination of BGPVS presence and diabetes, cerebral microbleed presence or lacune presence individually (*Table 4*). The result of each analysis was similar to that of the main multivariable model. We also undertook a sensitivity analysis to investigate the effect of dichotomising PVS as 0 – 20 or >20, rather than 0 – 10 or >10. Using this threshold, we did not find an association between higher BGPVS or CSOPVS counts and sICH (BGPVS: HR 1.0, 95% CI 0.13 – 7.5; CSOPVS: HR 1.3, 95% CI 0.36 – 4.6); however, few participants in our study had counts >20 in either location (*Table 2*), and confidence intervals for both estimates were wide.

For each model, visual inspection of log-log plots suggested no violation of the proportional hazards assumption. Although post-estimation tests provided some evidence that the assumption was violated for hypertension (p = 0.037), the estimate of the hazard ratio for sICH for hypertension provided no evidence for an association, and hypertension was not included in our multivariable model.

Discussion

Our main finding is an association between enlarged PVS within the basal ganglia, but not centrum semiovale, and OAC-ICH, independent of major vascular risk factors and other markers of cerebral small vessel disease. The estimate and 95% confidence interval of the hazard ratio was consistent with a clinically meaningful association, and was highly

statistically significant, though lacked precision. Although preliminary, our finding raises the possibility that enlarged BGPVS might be a clinically-relevant marker of OAC-ICH risk. Other studies have provided supportive observational evidence that incorporating small vessel disease markers, specifically CMB presence and WMH severity, can improve the performance of clinical risk scores for ICH [11,12], and the current analysis suggests that incorporating BGPVS status into these scores might usefully be investigated. An advantage of BGPVS status as a marker might be that it can be quantified on axial T2 imaging, a routine component of nearly all clinical MRI brain imaging.

Our findings add to the evidence linking enlarged PVS to cerebrovascular disease, but why PVS enlargement might occur in the setting of hemorrhage-prone cerebral small vessel disease remains unclear. PVS enlargement might reflect extravasation of fluid across damaged small vessel walls, possibly compounded by recruitment of inflammatory cells to the perivascular space, where they might promote further loss of blood-brain barrier integrity and impair perivascular fluid transport [20]. In cerebral amyloid angiopathy, perivascular aggregation of amyloid-beta may also impair drainage [21], but this is less likely to mediate the association between BGPVS and ICH we observed. It is possible that more advanced cerebral small vessel disease might lead directly to PVS enlargement through ischemic brain atrophy. We consider this less likely, as we corrected for a measure of overall cerebral atrophy, and observed an association which was independent of other cerebral small vessel disease markers, more consistent with BGPVS enlargement being a sensitive marker or early feature of cerebral small vessel disease. Finally, the association between BGPVS and ICH might be mediated by a shared underlying mechanism. For example, arterial stiffening has recently been associated with BGPVS [22], adjusted for major vascular risk factors, and also with deep ICH cross-sectionally and new CMB formation prospectively [23,24]. By reducing damping of the cardiac impulse and increasing transmission of pulsatile force to small cerebral arteries [25],

arterial stiffening might increase ICH risk, and promote PVS formation by altering small vessel pulsatility, thought to be a key driver of perivascular fluid transport [26,27].

Unexpectedly, we did not find an association between CSOPVS and sICH, despite evidence linking CSOPVS to cerebral amyloid angiopathy. We considered whether CSOPVS might simply be more difficult to measure reliably than BGPVS, leading to increased statistical noise and difficulty in detected any associations which do exist, but our excellent interrater reliability for both BGPVS and CSOPVS argues against this. More likely explanations include the low specificity of the association between CSOPVS and CAA, as CSOPVS enlargement also occurs in Alzheimer's disease without clinical CAA, and the low proportion of our study population (3%) who met modified Boston criteria for CAA, probably because such patients are not generally viewed as eligible for anticoagulation. Lastly, differences in regional vascular anatomy might contribute. Whereas the hemispheric white matter is supplied by penetrating branches of distal cortical arteries, the basal region of the brain is supplied by small perforating arteries which arise directly from large cerebral arteries. These vessels are therefore exposed to higher peak blood pressures [28], and so to the effects of systemic hypertension and, potentially, arterial stiffening. BGPVS enlargement might therefore be a more sensitive marker of these processes than CSOPVS.

As a secondary analysis of CROMIS-2 (AF), our study has methodological strengths: this was a large, multicenter prospective inception cohort study, recruiting a population similar in age, prevalence of vascular risk factors, and stroke severity, to the overall case mix of UK stroke units[29]. We obtained a >97% follow-up rate, and sICH events were adjudicated centrally without knowledge of CMB or PVS status. The MR imaging protocol was standardized between sites, and imaging markers were rated blinded to sICH during follow-up. We obtained substantial or excellent interrater agreement for key small vessel disease markers.

Our study has limitations, which we acknowledge. Most importantly, as a *post hoc* analysis, our results should be considered hypothesis-generating. The need for verification of our findings in an independent cohort is emphasised by the low number of outcome events observed, although we attempted to limit overfitting of our multivariable regression model by using a variable-selection procedure, and undertook additional sensitivity analyses. We included a clinical history of hypertension as an independent variable in our analysis, but we lacked data on BP control prior to or during the study, as well as details of anticoagulation control intensity for warfarin-treated patients, and adherence to anticoagulation for all participants. As eligibility for anticoagulation was an inclusion criterion for the study, our cohort might not be fully representative of the overall population of AF patients in whom anticoagulation is considered, and although study-specific imaging was performed after the decision to treat with anticoagulation was made, we cannot exclude the possibility that patient selection to our study may have been influenced by the results of imaging already performed as part of clinical care. The generalizability of our result may be further affected by our predominantly (95%) Caucasian study population, and the low proportion of patients taking direct oral anticoagulants (37%), which are increasingly preferred to warfarin in clinical practice due to their lower risk of ICH. Of the 14 ICH events observed in our study, 12 were in warfarin-treated patients.

As well as validating our findings, further study in a large independent cohort is needed to allow precise estimation of the strength of the association between BGPVS and OAC-ICH, and investigation of its association with BGPVS count or score, rather than the dichotomized rating used in this study. We failed to observe an association between >20 BGPVS and sICH, in contrast to a previous study [10], which we attribute to the low prevalence of higher PVS counts in our study and the small number of outcome events observed. However, the relationship between BGPVS count and sICH might also be non-linear, showing a 'threshold'

effect, and larger, better-powered studies might clarify this. Such studies might also investigate the relationship between PVS and different locations of sICH (for example, lobar vs deep/infratentorial intracerebral haemorrhage, or intracerebral vs subdural or subarachnoid haemorrhage), which have different biological mechanisms.

The clinical importance of our finding will depend on whether adding BGPVS status to existing ICH risk models can improve their performance, which we chose not to investigate in our cohort due to the risk of overfitting, and clarification of whether BGPVS are also associated with ischaemic stroke, and the strength of this association, if present, relative to that with ICH. This information is needed to establish whether BGPVS status should influence the selection of pharmacological and non-pharmacological treatments for stroke prevention in patients with AF in clinical practice. Large-scale global collaboration between cohort studies of OAC-related ICH, such as the Microbleeds International Collaborative Network (MICON) [30], might provide a means by which to investigate these unanswered questions.

Appendix 1: Authors

Name	**Location**	**Contribution**
Jonathan G Best, MRCP	University College London	Design of study; analysis and interpretation of data; drafting the manuscript for intellectual content.
Carmen Barbato, MD	University College London	Analysis and interpretation of data; revising manuscript for intellectual content
Gareth Ambler, PhD	University College London	Analysis of data; revising manuscript for intellectual content
Houwei Du, MD	Fujian Medical	Analysis of data; revising manuscript for

	University	intellectual content
Gargi Banerjee, PhD, MRCP	University College London	Analysis of data; revising manuscript for intellectual content
Duncan Wilson, PhD	University College London	Analysis of data; revising manuscript for intellectual content
Clare Shakeshaft, MSc	University College London	Major role in acquisition of data; revising manuscript for intellectual content
Hannah Cohen, MD, FRCP	University College London	Revising manuscript for intellectual content
Tarek A Yousry, FRCR	University College London	Revising manuscript for intellectual content
Rustam Al-Shahi Salman, PhD	University of Edinburgh	Revising manuscript for intellectual content
Gregory Y H Lip, FRCP	University of Liverpool, UK; Liverpool Heart and Chest Hospital, UK; Aalborg University, Denmark	Revising manuscript for intellectual content
Henry Houlden, MRCP	University College London	Revising manuscript for intellectual content
Martin M Brown, FRCP	University College London	Revising manuscript for intellectual content
Keith W Muir, MD, FRCP	University of Glasgow	Revising manuscript for intellectual content
Hans Rolf Jäger,	University College	Analysis of data; revising manuscript for

MD, FRCR	London	intellectual content
David J Werring, PhD	University College London	Study conceptualisation and design; interpretation of data; revising manuscript for intellectual content

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Table 1: characteristics of study population

Comparison of characteristics of participants included in analysis to those excluded for missing at least one variable. Values show prevalence for categorical variables, and mean (SD) or median (IQR) for continuous variables.

Characteristic		**Included (n = 1386)**	**Excluded (n = 61)**
Age		75.8 (10.4)	78.2 (9.2)
Female sex		575/1386 (41.5%)	36/61 (59.0%)
Hypertension		876/1386 (63.2%)	30/39 (76.9%)
Diabetes		229/1386 (16.5%)	13/59 (22.03%)
>10 BGPVS		363/1386 (26.2%)	14/48 (29.2%)
>10 CSOPVS		665/1386 (48.0%)	23/48 (47.9%)
Lacune presence		286/1386 (20.6%)	9/41 (22.0%)
CMB presence		288/1386 (20.8%)	16/61 (26.2%)
ARWMC score		1 (0 – 3)	1 (0 – 3)
cSS presence		5/1386 (0.35%)	0 (0%)
GCA score	0	461/1386 (33.3%)	17/59 (28.8%)
	1	613/1386 (44.2%)	29/59 (49.2%)
	2 - 3	312/1386 (22.5%)	13/59 (22.0%)
sICH during follow-up		14/1386 (1%)	0/61 (0%)

Table 2: characteristics of patients with and without sICH

Comparison of characteristics of participants included in analysis with and without sICH during follow-up. Values show prevalence for categorical variables, and mean (SD) or median (IQR) for continuous variables.

Characteristic		**No sICH (n = 1372)**	**sICH (n = 14)**
Age		75.8 (10.4)	78.6 (10.5)
Female sex		570/1372 (41.6%)	5/14 (35.7%)
Hypertension		868/1372 (63.3%)	8/14 (57.1%)
Diabetes		223/1372 (16.3%)	6/14 (42.9%)
>10 BGPVS		352/1372 (25.7%)	11/14 (78.6%)
BGPVS count	0	62/1372 (4.5%)	0/14 (0%)
	1 - 10	958/1372 (69.8%)	3/14 (21.4%)
	11 - 20	247/1372 (18.0%)	10/14 (71.4%)
	21 - 40	86/1372 (6.3%)	1/14 (7.1%)
	>40	19/1372 (1.4%)	0/14 (0%)
>10 CSOPVS		658/1372 (48.0%)	7/14 (50.0%)
CSOPVS count	0	80/1372 (5.8%)	0/14 (0.0%)
	1 - 10	634/1372 (46.2%)	7/14 (50.0%)
	11 - 20	421/1372 (30.7%)	4/14 (28.6%)
	21 - 40	197/1372 (14.4%)	3/14 (21.4%)
	>40	40/1372 (2.9%)	0/14 (0.0%)
Lacune presence		280/1372 (20.4%)	6/14 (42.9%)
CMB presence		281/1372 (20.5%)	7/14 (50.0%)
CMB	Deep	113/1372 (8.2%)	1/14 (7.1%)

distribution	Lobar	102/1372 (7.4%)	3/14 (21.4%)
	Mixed	66/1372 (4.8%)	3/14 (21.4%)
ARWMC score		1 (0 – 3)	1.5 (0 – 5)
cSS presence		4/1372 (0.3%)	1/14 (7.1%)
GCA score	0	455/1372 (33.2%)	6/14 (42.9%)
	1	607/1372 (44.2%)	6/14 (42.9%)
	2 - 3	310/1372 (22.6%)	2/14 (14.3%)

Table 3: Associations between variables and sICH

Hazard ratios (with 95% CI) in univariable analysis are shown for each study variable. Multivariable hazard ratios refer to a model incorporating all variables with $p < 0.2$ in univariable analysis.

Characteristic	Univariable HR	P value	Multivariable HR	P value
Age	1.04 (0.98 – 1.09)	0.22	NA	NA
Female sex	0.82 (0.27 – 2.43)	0.72	NA	NA
Hypertension	0.79 (0.28 – 2.29)	0.67	NA	NA
Diabetes	3.88 (1.35 – 11.2)	0.012	3.91 (1.34 – 11.4)	0.012
>10 BGPVS	10.8 (3.01 – 38.7)	0.000	8.96 (2.41 – 33.4)	0.001
>10 CSOPVS	1.06 (0.37 – 3.01)	0.92	NA	NA
Lacune presence	2.97 (1.03 – 8.57)	0.044	1.54 (0.52 – 4.59)	0.43
CMB presence	3.80 (1.33 – 10.8)	0.013	2.61 (0.90 – 7.54)	0.077
ARWMC score	1.07 (0.86 – 1.34)	0.55	NA	NA
GCA score: 1	0.76 (0.25 – 2.37)	0.64	NA	NA
2 - 3	0.52 (0.11 – 2.59)	0.43	NA	NA

Table 4: sensitivity analyses

Multivariable hazard ratio (with 95% CI) is shown for each variable in each model tested.

Model	Components	Multivariable HR
1	>10 BGPVS	11.5 (3.20 – 41.3)
	Diabetes	4.37 (1.51 – 12.6)
2	>10 BGPVS	9.46 (2.6 – 34.2)
	CMB presence	2.84 (0.99 – 8.17)
3	>10 BGPVS	9.55 (2.60 – 35.1)
	Lacune presence	1.77 (0.60 – 5.20)

Figure 1: Study flowchart

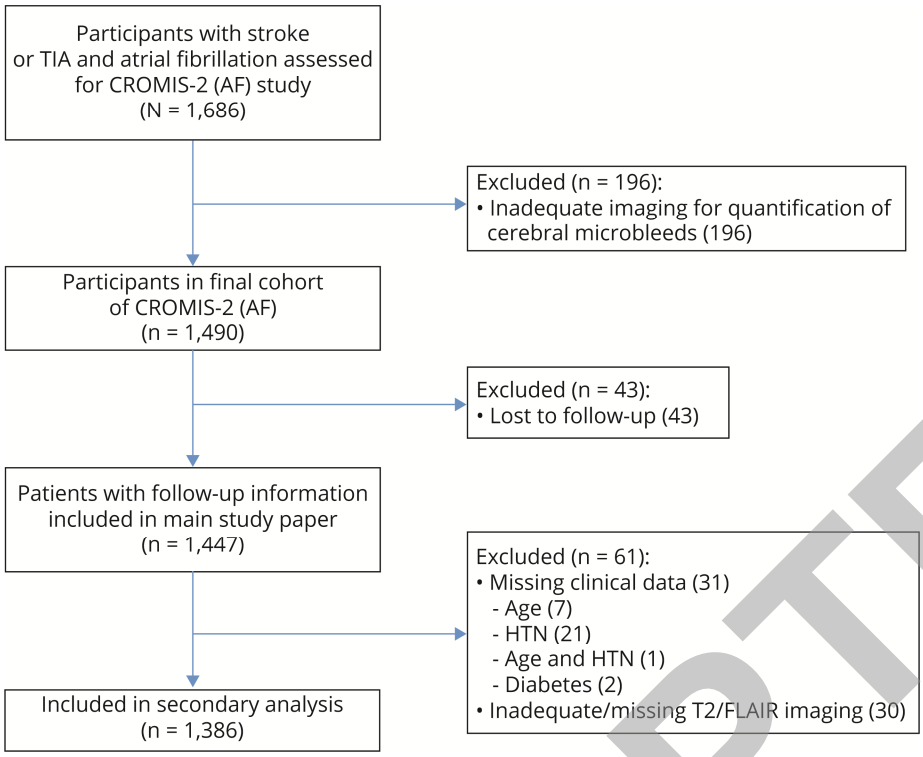
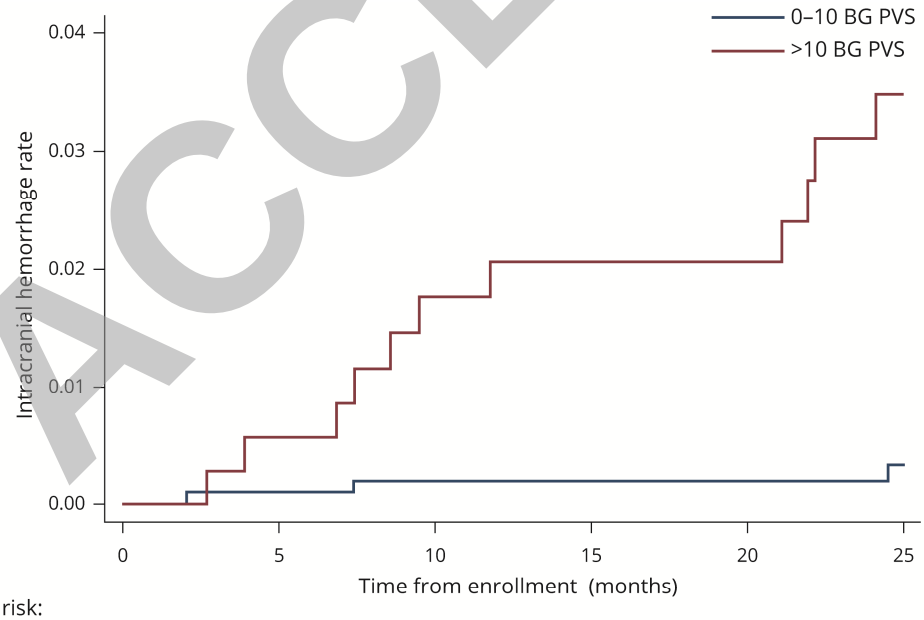


Figure 2: Cumulative probability of symptomatic ICH by BGPVS rating



Number at risk:

0–10 BG PVS	1,023	987	959	887	860	625
>10 BG PVS	363	343	327	296	285	206

Association of enlarged perivascular spaces and anticoagulant-related intracranial hemorrhage

Jonathan G Best, Carmen Barbato, Gareth Ambler, et al.

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